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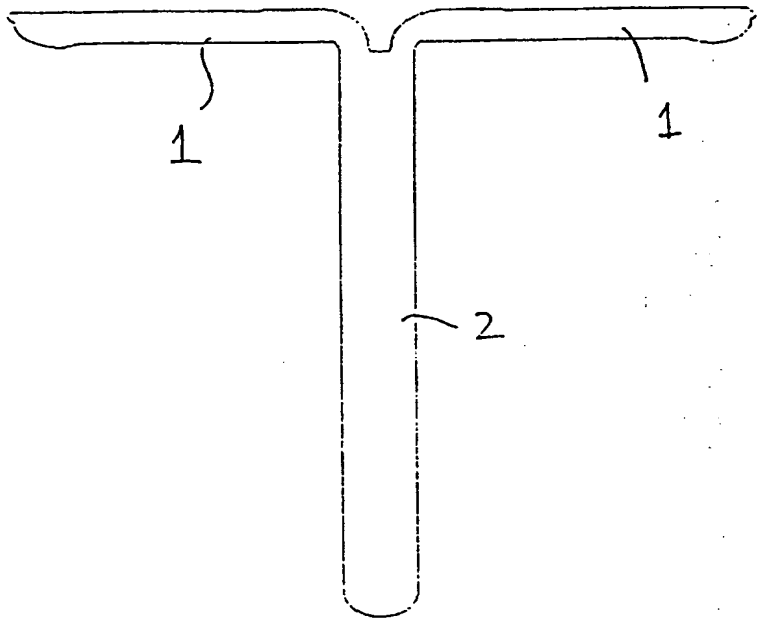

(57) Abstract

An intra vaginal device for delivering a pharmaceutical agent (e.g. progesterone) into a recipient mammal. The active agent is carried in a matrix of a biodegradable polymer (such as poly ϵ–caprolactone or a starch–like polysaccharide) having an ability to provide (without reliance on a supporting spine) desired retention characteristics of a variable geometry retention device, an appropriate release profile during a finite insertion period and biodegradability upon removal from the mammal.

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BIODEGRADABLE INTRA VAGINAL DEVICES

The present invention relates to improvements in and/or relating to intra vaginal devices or inserts.

Our PCT/NZ97/00052 (published as WO 97/40776) discloses a variety of different forms of intra vaginal device of a variable geometry type for retention within the intra vaginal cavity of an animal. Such devices hitherto have primarily involved the use of a silicone rubber composition which as a matrix has been impregnated with the active pharmaceutical agent (eg; progesterone). In the variable geometry type devices typified by the CIDR™ devices of this company the impregnated matrix has primarily been supported on a spine of a resilient material such as nylon, the resilience of which is utilised for the variable geometry retention characteristics notwithstanding that such spine is usually fully overlaid with the impregnated matrix.

Various polymers possessing the ability to undergo biodegradation have been used to deliver pharmaceutical agents. A class of polymers possessing this characteristic and extensively utilized for the delivery of pharmaceutical agents are the polyesters. Examples of these polymers include poly lactic acid, poly glycolic acid, poly (ε-caprolactone) and various co-polymers of lactide, glycolide and ε-caprolactone.

Pharmaceutical products utilizing these polymers are typically formulated as microspheres, microcapsules, films, rods or blocks. Retention within a body cavity has been achieved by a number of methods; the addition of dense fillers, injections or surgical implantation into muscle or subcutaneous area.

The present invention relates to a device or insert designed to deliver progesterone over an extended period of time (2 to 20 days) upon insertion into the vagina of animals such as cattle, sheep, horses, pigs, goats, buffalo or deer. The device or insert is retained within the vagina by means of a flexible geometric arrangement (eg; of the arms and body).

Upon completion of treatment the device is removed and disposed of in a manner that preferably capitalizes upon the biodegradable properties of the polymer.

We have determined that biodegradable polymers typified by poly(ε-caprolactone) or a starch like saccharide can be appropriately impregnated with an intra vaginally

effective active agent [such as progesterone (e.g. in concentration of from 5% to 70% w/w)] so as to provide appropriate *in vivo* release characteristics for the active agent over a period of intra vaginal retention required by the particular procedure whereupon, after extraction, the material is readily biodegradable following removal from the animal.

Surprisingly it has also been found that a polymer such as a poly (ε-caprolactone) can be moulded notwithstanding its being impregnated with the active agent to provide not only the impregnated matrix but also to provide the variable geometry device without an obligatory presence of a spine or the like such as in the prior art devices. Similarly, starch like saccharides have been found to be capable of being shaped to the same effect.

Accordingly in a first aspect the present invention consists in **a device or insert** for insertion into the vagina of a mammal, said device or insert consisting of a biodegradable polymer containing a pharmaceutical agent.

Preferably the device or insert is vaginally retainable (preferably by variable geometry means at least partially dependent on the resilience of the biodegradable polymer) for at least 5 days in a target species.

Preferably the agent is progesterone in the concentration of 5 to 70% w/w.

Preferably the polymer is or includes poly (ε-caprolactone).

Alternatively the polymer is or includes a starch-like polysaccharide.

In other forms the polymer may be a blend of the options and/or another polymer.

Preferably said biodegradable polymer includes therein both a cyclodextrin and an intra vaginally effective active ingredient.

The term "intra vaginally effective active agent" means any compound or composition or complex that by means of delivery into the vaginal cavity of a mammal can be absorbed systemically by the mammal therefrom so as to achieve or suppress some physiological effect. Examples include progesterone (eg: for oestrus synchronisation and other purposes) and oxytocin (eg: for milk let down).

The term "cyclodextrin" includes any suitable cyclodextrin or mixtures thereof, eg: α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin and hydroxypropyl β-cyclodextrin.

Preferably the cyclodextrin(s) comprise from 5 to 70% $^{w}/_{w}$.

Preferably the absorption enhancing agent is hydroxypropyl β-cyclodextrin in the concentration of 5 to 70% $^{w}/_{w}$.

Preferably the device is of such geometry to facilitate retention in the vagina.

Preferably the agent does not appear as a fine powder or crystals upon the surface of the device.

In another aspect the present invention is **an intra vaginal device or insert** for a target species mammal comprising or including an intra vaginally insertable, retainable and removable mass of at least primarily one or both of poly (ε-caprolactone) and a mouldable biodegradable starch-like polysaccharide, the mass by virtue of its resilience being of variable geometry which allows the intra vaginal insertion, retention and removal,

wherein said mass includes therein sufficient progesterone therein such that for a target species a blood serum level of progesterone of greater than $2^{ng}/_{ml}$ for a period of at least 5 days can follow intra vaginal insertion thereof and wherein after removal the mass is biodegradable after removal from the animal.

Preferably said target species is selected from cattle, sheep, horses, pigs, goats, buffalo and deer.

Preferably said device or insert includes no supporting spine (eg; nylon or polyester).

Preferably the progesterone inclusion is sufficient to deliver progesterone for a period from 2 to 20 days.

Optionally said mass may include cyclodextrin.

In a further aspect the present invention consists in **the use** or **methods of use** of such a device or any device of the present invention.

The present invention also consists in **a method of manufacture of an intra vaginal device** which results in any device in accordance with the present invention. In another aspect the invention consists in **a method of manufacture of an intra vaginal device** which comprises the step of including in a mouldable biodegradable polymer matrix both a cyclodextrin and an intra vaginally effective agent.

In still another aspect the invention consists in **the use** inter alia **for animal group oestrus synchrony purposes** of devices or inserts of the present invention.

Preferably said use is intra vaginal use for a period of from 2 to 20 days and said device has a capability in the target species mammal of providing for at least 5 days (if intra vaginally inserted for at least about 5 days) a blood serum level of progesterone of greater than $2^{ng}/_{ml}$.

Preferably all polymer(s) of the said mass (if all, as is preferred, is to moulded) can be moulded without use of conditions prejudicial to the pharmaceutical agent and any cyclodextrin (or for that matter, any other absorption enhancing agent) present.

In still a further aspect the invention consists in **a method of achieving with an animal (or group of animals) a blood serum level of progesterone of greater than $2^{ng}/_{ml}$ for a period of at least 5 days,** said method comprising inserting and retaining in the or each animal for at least the at least 5 day period a device or insert of the present invention.

We have found that the biodegradable polymers of choice are capable of being effectively impregnated with the pharmaceutical agent and optionally an absorption enhancement agent, being effectively moulded into the form of an intra vaginal device or insert of a kind reliant on variable geometry for retention, providing over the finite insertion period an appropriate tract to provide a desired pharmacological effect without detriment from any propensity of the polymer(s) to *in vivo* biodegrade, and, upon removal much lower in pharmaceutical agent content (see WO 97/40776), of providing no long term disposal problem owing to the propensity of the polymer(s) to biodegrade after removal from the animal.

Preferred forms of the present invention will now be described with reference to the accompanying drawings in which:

Figure 1 shows a device of variable geometry (the geometry being variable much in the way as discussed in WO 97/40776) but without a need for a spine of a dissimilar material (although if desired that can optionally be present),

Figure 2 shows an *in vitro* cumulative progesterone release against the square-root-of-time (inserts manufactured from poly (ε-caprolactone) (thin line) or silicone (thick line)).

Figure 3 shows an average plasma progesterone concentration against time following two rounds of vaginal treatment with a silicone insert of 134 cm^2 surface area

(□) or a poly (ε-caprolactone) insert of 105 cm^2 surface area (■), both of which contain 10% $^w/_w$ progesterone (error bars are standard error means (n-12 for silicone inserts, n=9 for poly (ε-caprolactone) inserts)),

Figure 4 shows a percentage of initial mass lost for drug-loaded (■) and blank (□) poly (ε-caprolactone) inserts stored in compost over time (the solid line is the suggested mass loss as per promotional literature supplied by the poly (ε-caprolactone) manufacturer (error bars are ranges (n=2)),

Figure 5 shows a percentage of tensile performance lost for drug-loaded (■) and blank(□) poly (ε-caprolactone) inserts buried in compost over time (the solid line is the suggested tensile performance loss as per promotional literature supplied by the manufacturer. (Error bars are ranges (n=2)),

Figure 6 shows plasma progesterone concentration against time following vaginal treatment for 7 days with a silicone insert of 134 cm^2 surface area (■), poly (ε-caprolactone) insert of 115 cm^2 surface area (□) or poly (ε-caprolactone) with lactose insert of 115 cm^2 surface area (○) (A final plasma sample was collected 6 hours after removal on day 7. (Error bars are standard error means (n=3)),

Figure 7 shows the percentage of initial mass lost for various poly (ε-caprolactone) formulations stored in compost over time [Poly (ε-caprolactone) (♦), poly (ε-caprolactone) with 10% $^w/_w$ progesterone (■), poly (ε-caprolactone) with 12.1% $^w/_w$ lactose and 10.47% $^w/_w$ progesterone (▲), poly (ε-caprolactone) with 37.2% $^w/_w$ β-cyclodextrin and 10.3% $^w/_w$ progesterone (x), poly (ε-caprolactone) with 43.8% $^w/_w$ hydroxypropyl β-cyclodextrin and 10% $^w/_w$ progesterone (*) or poly (ε-caprolactone) with 39.9% $^w/_w$ γ-cyclodextrin and 9.7% $^w/_w$ progesterone (●). (Error bars are ranges (n=2))], and

Figure 8 shows plasma progesterone concentration against time following vaginal treatment for 7 days with a Mater-Bi insert of 58 cm^2 surface area with (■) or without (●) the addition of 20% w/w NaCl. (Error bars are ranges (n=2)).

The choice of a resilient mouldable or shapable "polymer" which is biodegradable is such that degradation of the impregnated matrix (but with a low residual active ingredient loading) will occur over time after removal from the animal after having served its purpose during an intra vaginal insertion of preferably from 2 to 20 days (eg;

about 7 days). Minimal degradation (if any) occurs during the period of insertion.

In the device of Figure 1 the device is wholly of the impregnated matrix which is poly (ε-caprolactone) impregnated with progesterone in the concentration of 5 to 70% w/w without any solid active pharmaceutical agent appearing as a fine powder or crystals on the surface of the device.

In Figure 1 the wings 1 are resilient with respect to the body 2 and in an intra vaginal injection mode can be reduced to a form or assume a position in an applicator in a known manner which facilitates insertion after which the resilience deploys the wings 1 to such condition as is required for retention. The resilience can be subsequently utilised to withdraw the device from within the vagina.

A suitable source of poly (ε-caprolactone) is that product TONE 767™ from Union Carbide Specialty Polymers and Products, Danbury, Ct, USA.

Starch-like polysaccharides that can likewise be impregnated and can be used for some or all of the device include MATER-Bi™ available from Novamont, Italy.

A preferred method of manufacturing of the device is as follows: Polymer poly ε-caprolactone, starch-like polysaccharide or a blend of the two are mixed with active into a mixing vat using a suitable compound, eg; surfactant to adhere the active to the surface of the polymer granules or the use of compound extruded material.. The polymer/active mixture is then loaded into the hopper of an injection moulding machine, and processed as a conventional thermoplastic, with machine set point parameters as per the technical recommendations of the polymer suppliers literature, and as per injection moulding standard practice.

Key processing set points for poly ε-caprolactone are: barrel temperatures ranging from 80 - 120°C with an injection pressure of 1600 bar. Total cycle time due to long cooling phase of approximately 55 seconds. Product is removed from the die and allowed to cool to equilibrium prior to packaging.

Preferably the performance of the device while inserted and its effect upon withdrawal is substantially as discussed in WO 97/40776 but with the advantages of (i) biodegradability after removal from the animal and (ii) the preferred omission of a spine of resilient material.

The preferred biodegradable polymers (typified by poly (ε-caprolactone) or a

starch like saccharide) can be appropriately impregnated with an intra vaginally effective active agent such as progesterone (eg: in concentration of from 5% to 70% w/w) and an absorption enhancing agent such as hydroxypropyl β-cyclodextrin (eg: in concentrations of from 5% to 70% w/w) so as to provide appropriate release characteristics for the active agent over the period of intra vaginal retention.

The preferred device is wholly of the impregnated matrix which is poly (ε-caprolactone) impregnated with hydroxypropyl β-cyclodextrin in the concentration of 5 to 70% w/w.

A suitable source of hydroxypropyl β-cyclodextrin is that product BETA W7 HP available from Wacker Chemicals Australia, Victoria, Australia.

A preferred method of manufacture of the device is as follows: Polymer (poly (ε-caprolactone), starch-like polysaccharide or a blend of the two) are mixed with active and absorption agent into a mixing vat. The polymer/active/absorption agent mixture is then loaded into the hopper of an injection moulding machine; and processed as a conventional thermoplastic, with machine set point parameters as per technical recommendations of the polymers suppliers literature, and as per injection moulding standard practice. Key processing points are: barrel temperatures ranging from 60 - 250°C with an injection pressure of 1600 bar. Total cycle time due and allowed to cool to equilibrium prior to packaging.

Figure 1 shows a device of variable geometry (the geometry being variable much in the way as discussed in WO 97/40776) but without a need for a spine of a dissimilar material (although if desired that can optionally be present),

When inserts of the type shown in Figure 1 manufactured from poly (ε-caprolactone) are subjected to an *in vitro* dissolution procedure to assess the release of progesterone they display release characteristics similar to the silicone CIDR-B™ insert, Figure 2.

Figure 2 shows an in vitro cumulative progesterone release against the square-root-of-time. Inserts manufactured from poly (ε-caprolactone) (thin line) or silicone (thick line).

When inserts of the type shown in Figure 1 manufactured from poly (ε-caprolactone) of surface area less than the silicone CIDR-B™ inserts are administered

to cattle and plasma samples collected for plasma progesterone concentration analysis slightly lower levels are observed, Figure 3.

Figure 3 shows an average plasma progesterone concentration against time following two rounds of vaginal treatment with a silicone insert of 134 cm^2 surface area (□) or a poly (ε-caprolactone) insert of 105 cm^2 surface area (■), both of which contain 10% $^w/_w$ progesterone. Error bars are standard error means (n-12 for silicone inserts, n=9 for poly (ε-caprolactone) inserts).

When inserts of the type depicted in Figure 1 manufactured from poly (ε-caprolactone) which container progesterone at 10 % $^w/_w$ or no progesterone are stored in compost for a period of 6 months the following mass losses are observed, Figure 4.

Figure 4 shows a percentage of initial mass lost for drug-loaded (■) and blank (□) poly (ε-caprolactone) inserts stored in compost over time. The solid line is the suggested mass loss as per promotional literature supplied by the poly (ε-caprolactone) manufacturer. Error bars are ranges (n=2).

When inserts of the type depicted in Figure 1 manufactured from poly (ε-caprolactone) which contain progesterone at 10 % $^w/_w$ or no progesterone are stored in compost for a period of 6 months the following tensile performance losses are observed, Figure 5.

Figure 5 shows a percentage of tensile performance lost for drug-loaded (■) and blank(□) poly (ε-caprolactone) inserts buried in compost over time. The solid line is the suggested tensile performance loss as per promotional literature supplied by the manufacturer. Error bars are ranges (n=2).

When inserts of the type shown in Figure 1 manufactured from poly (ε-caprolactone) of surface area similar to our silicone CIDR-B™ insert (disclosed in aforementioned WO 97/40776) are administered to cattle and plasma samples collected from plasma progesterone concentration analysis similar levels are observed. See Figure 6.

Figure 6 shows plasma progesterone concentration against time following vaginal treatment for 7 days with a silicone insert of 134 cm^2 surface area (■), poly (ε-caprolactone) insert of 115 cm^2 surface area (□) or poly (ε-caprolactone) with lactose insert of 115 cm^2 surface area (○). A final plasma sample was collected 6 hours after

removal on day 7. Error bars are standard error means (n=3).

When inserts of the type depicted in Figure 1 manufactured from poly (ε-caprolactone) which contain various excipients are stored in compost for a period of 6 months the mass losses shown in Figure 7 are observed.

Figure 7 shows the percentage of initial mass lost for various poly (ε-caprolactone) formulations stored in compost over time. Poly (ε-caprolactone) (♦), poly (ε-caprolactone) with 10% $^{w}/_{w}$ progesterone (■), poly (ε-caprolactone) with 12.1% $^{w}/_{w}$ lactose and 10.47% $^{w}/_{w}$ progesterone (▲), poly (ε-caprolactone) with 37.2% $^{w}/_{w}$ β-cyclodextrin and 10.3% $^{w}/_{w}$ progesterone (x), poly (ε-caprolactone) with 43.8% $^{w}/_{w}$ hydroxypropyl β-cyclodextrin and 10% $^{w}/_{w}$ progesterone (*) or poly (ε-caprolactone) with 39.9% $^{w}/_{w}$ γ-cyclodextrin and 9.7% $^{w}/_{w}$ progesterone (●). Error bars are ranges (n=2).

When inserts are the type shown in Figure 1 manufactured using polysaccharide are administered to cattle and plasma samples collected for plasma progesterone concentration analysis the levels of Figure 8 are observed.

Figure 8 shows plasma progesterone concentration against time following vaginal treatment for 7 days with a Mater-Bi insert of 58 cm^2 surface area with (■) or without (●) the addition of 20% w/w NaCl. Error bars are ranges (n=2).

WHAT WE CLAIM IS:

1. **A device or insert** for insertion into the vagina of a mammal, said device or insert consisting of a biodegradable polymer containing a pharmaceutical agent.

2. A device or insert of claim 1 which is vaginally retainable for at least 2 days in a target species.

3. A device or insert of claim 1 or 2 wherein it is retainable by reliance on an ability to assume variable geometries some of which are dependent on the resilience of the biodegradable polymer.

4. A device or insert of claim 1 wherein the agent is progesterone.

4. A device or insert of claim 4 wherein the progesterone comprises from 5 to 70% $^{w}/_{w}$.

5. A device or insert of claim 1 wherein the polymer is or includes poly (ε-caprolactone).

7. A device or insert of claim 1 wherein the polymer is or includes a starch-like polysaccharide.

8. A device or insert of claim 7 or 8 wherein said biodegradable polymer includes therein both a cyclodextrin and an intra vaginally effective active ingredient

said intra vaginally effective active agent being any compound or composition or complex that by means of delivery into the vaginal cavity of a mammal can be absorbed systemically by the mammal therefrom so as to achieve or suppress some physiological effect.

9. A device or insert of any one of the preceding claims wherein said biodegradable polymer includes therein both a cyclodextrin and an intra vaginally effective active ingredient

said intra vaginally effective active agent being any compound or composition or complex that by means of delivery into the vaginal cavity of a mammal can be absorbed systemically by the mammal therefrom so as to achieve or suppress some physiological effect.

10. A device or insert of claim 9 wherein the cyclodextrin(s) comprise from 5 to 70 $^{w}/_{w}$.

11. A device or insert of any one of the preceding claims wherein the agent does not

appear as a fine powder or crystals upon the surface.

12. **An intra vaginal device or insert** for a target species mammal comprising or including an intra vaginally insertable, retainable and removable mass of at least primarily one or both of poly (ε-caprolactone) and a mouldable biodegradable starch-like polysaccharide, the mass by virtue of its resilience being of variable geometry which allows the intra vaginal insertion, retention and removal,

wherein said mass includes therein sufficient progesterone therein such that for a target species a blood serum level of progesterone of greater than $2^{ng}/_{ml}$ for a period of at least 5 days can follow intra vaginal insertion thereof and wherein after removal the mass is *in vitro* biodegradable.

13. A device or insert of claim 12 wherein said target species is selected from cattle, sheep, horses, pigs, goats, buffalo and deer.

14. A device or insert of claim 12 or 13 absent of any supporting spine.

15. A device or insert of any one of claims 12 to 14 wherein the progesterone inclusion is sufficient to deliver progesterone for a period from 2 to 20 days.

16. A device or insert of any one of claims 12 to 15 wherein said mass may include cyclodextrin.

17. **The use** or **methods of use** of a device or insert of any one of the preceding claims.

18. **A method of manufacture of an intra vaginal device** which results in a device or insert in accordance with any one of claims 1 to 11.

19. **A method of manufacture of an intra vaginal device or insert** which comprises the step of including in a mouldable biodegradable polymer matrix both a cyclodextrin and an intra vaginally effective agent and thereafter forming the device or insert therefrom.

20. **The use** inter alia **for animal group oestrus synchrony purposes** of devices or inserts of any one of claims 1 to 16.

21. A use of claim 20 wherein said use is intra vaginal use for a period of from 2 to 20 days and said device has a capability in the target species mammal of providing for at least 5 days (if intra vaginally inserted for at least about 5 days) a blood serum level of progesterone of greater than $2^{ng}/_{ml}$.

22. **A method of achieving with an animal (or group of animals) a blood serum level of progesterone of greater than 2 $^{ng}/_{ml}$ for a period of at least 5 days,** said method comprising inserting and retaining in the or each animal for at least the at least 5 day period a device or insert of any one of claims 1 to 16.

23. An intra vaginally device or insert substantially as hereinbefore described with reference to any one or more of the accompanying drawings.

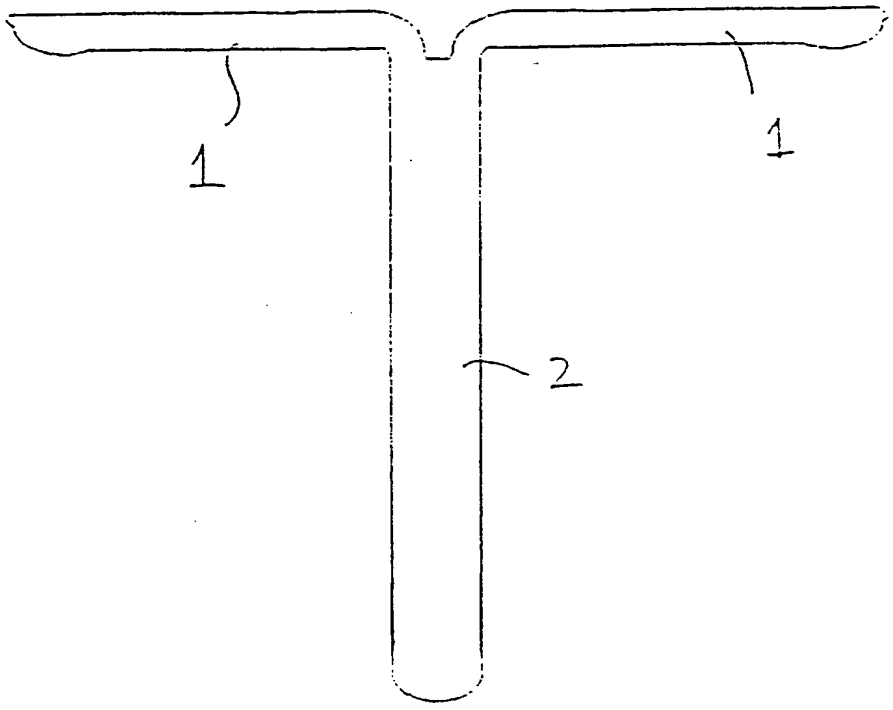

FIGURE 1

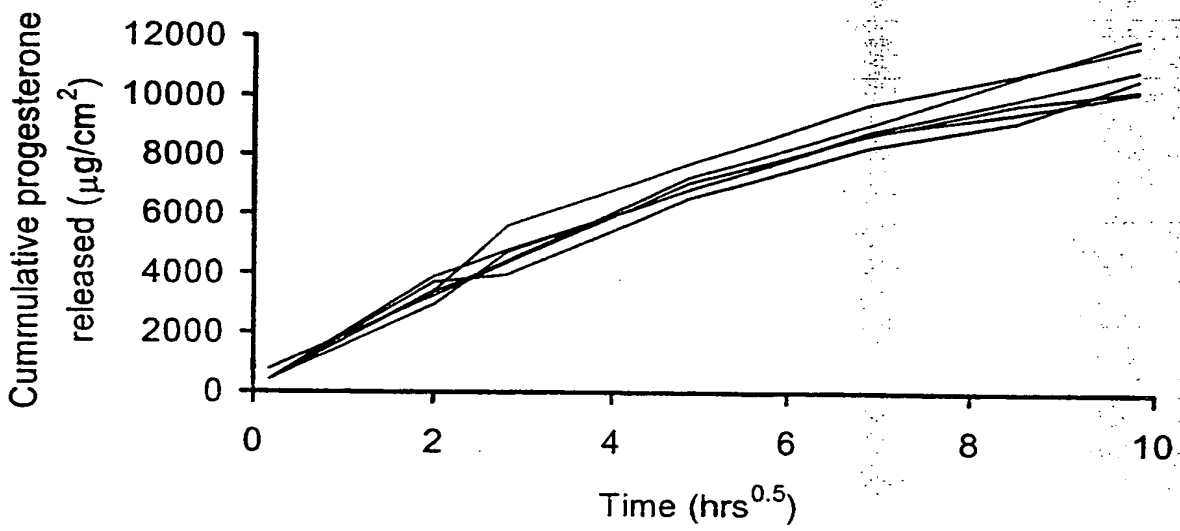

FIGURE 2

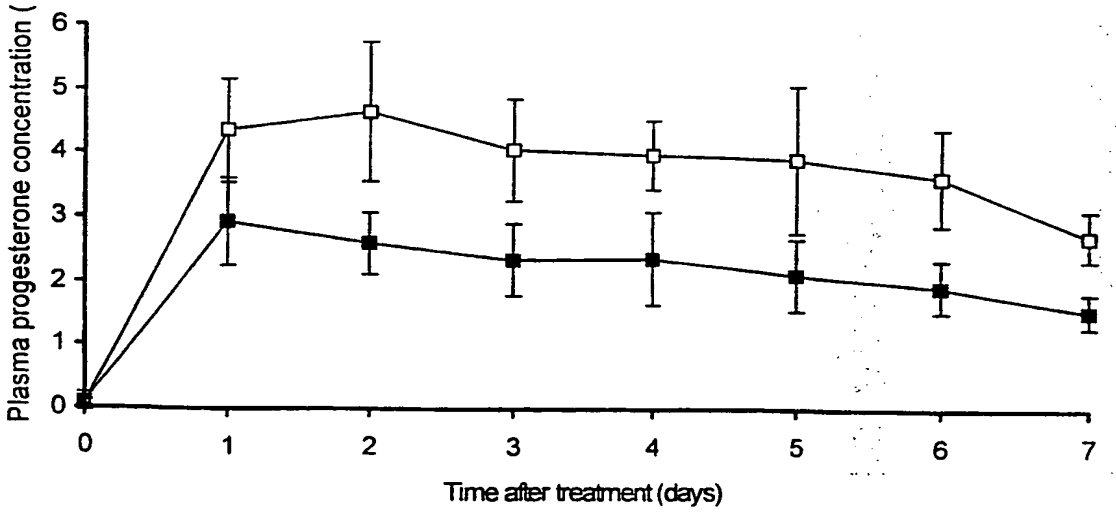

FIGURE 3

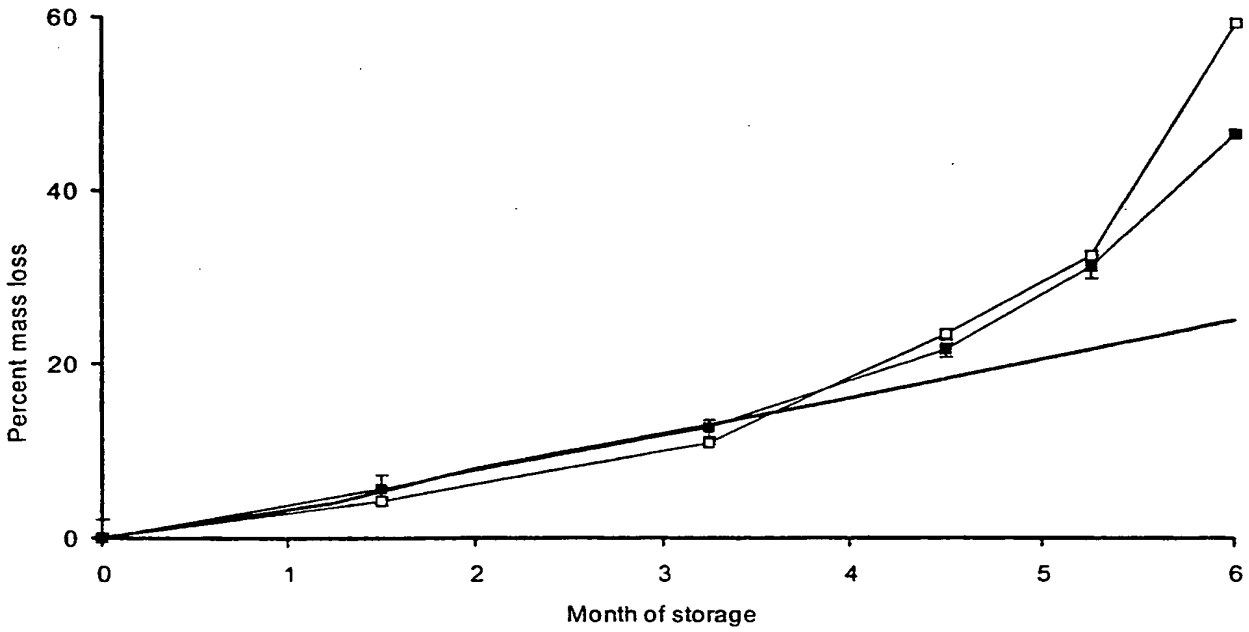

FIGURE 4

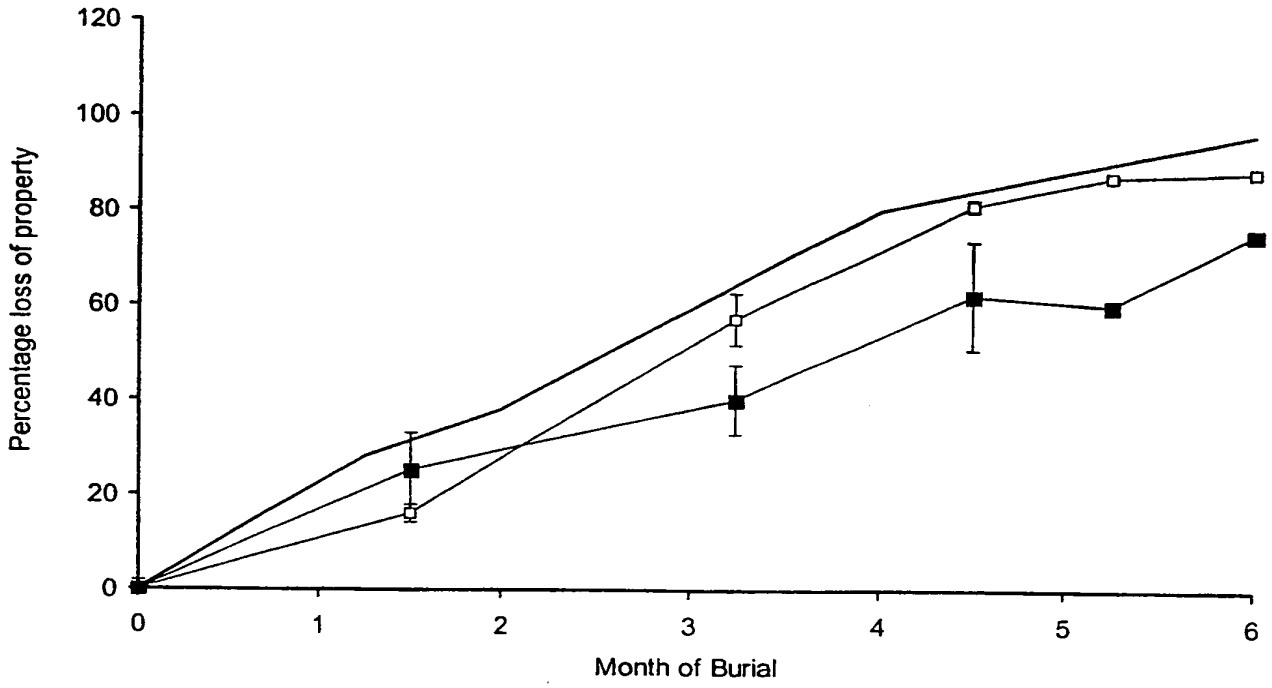

FIGURE 5

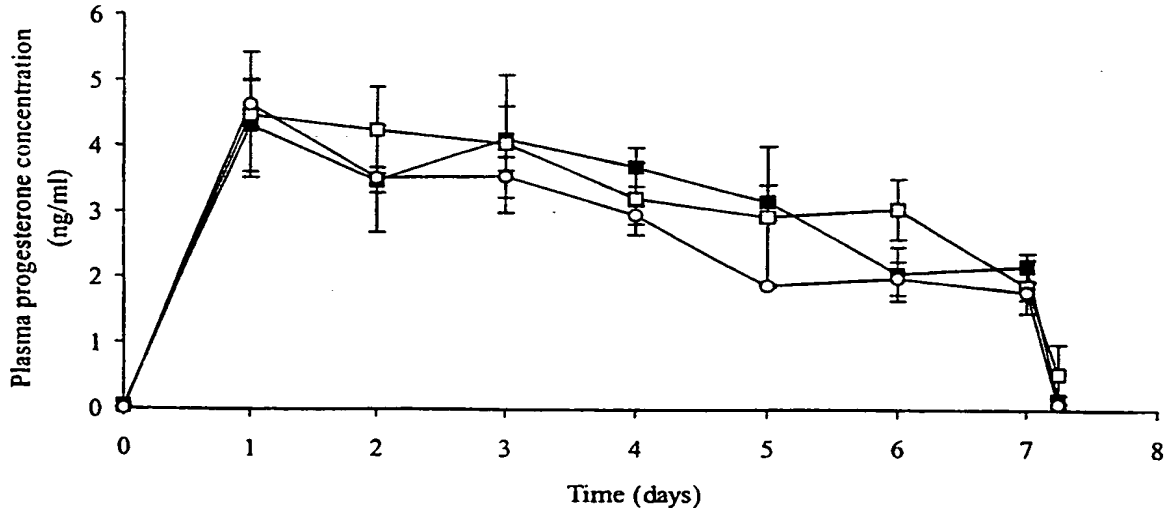

FIGURE 6

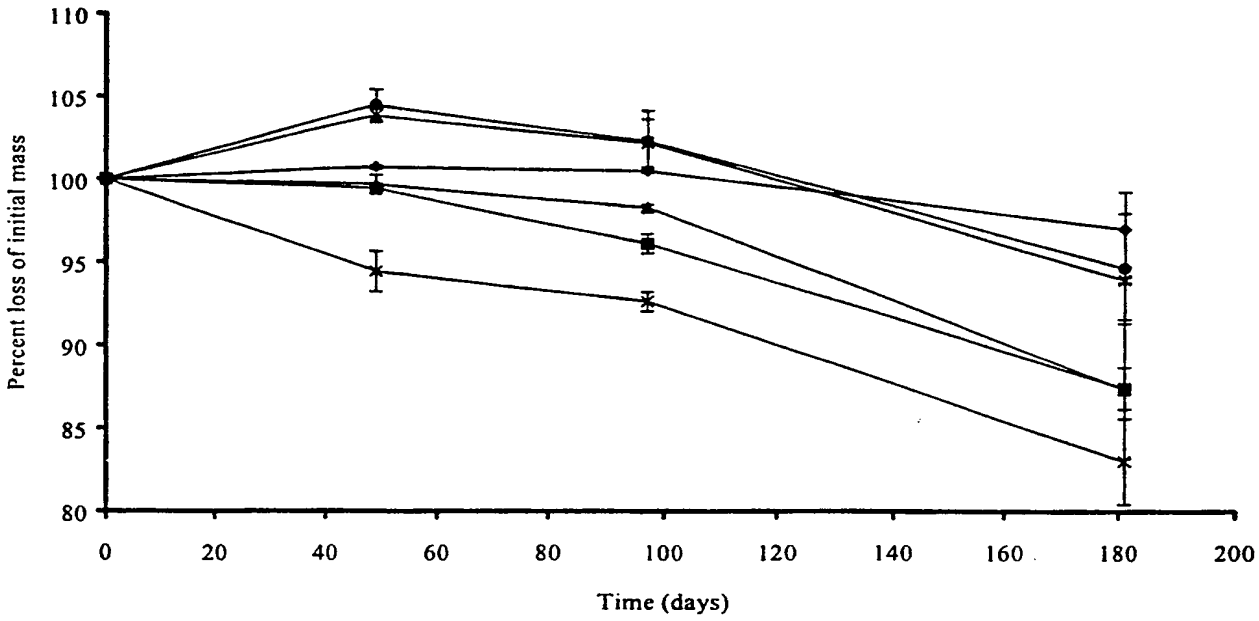
110
105
100
95
90
85
80
Percent loss of initial mass
0
20
40
60
80
100
120
140
160
180
200
Time (days)

FIGURE 7

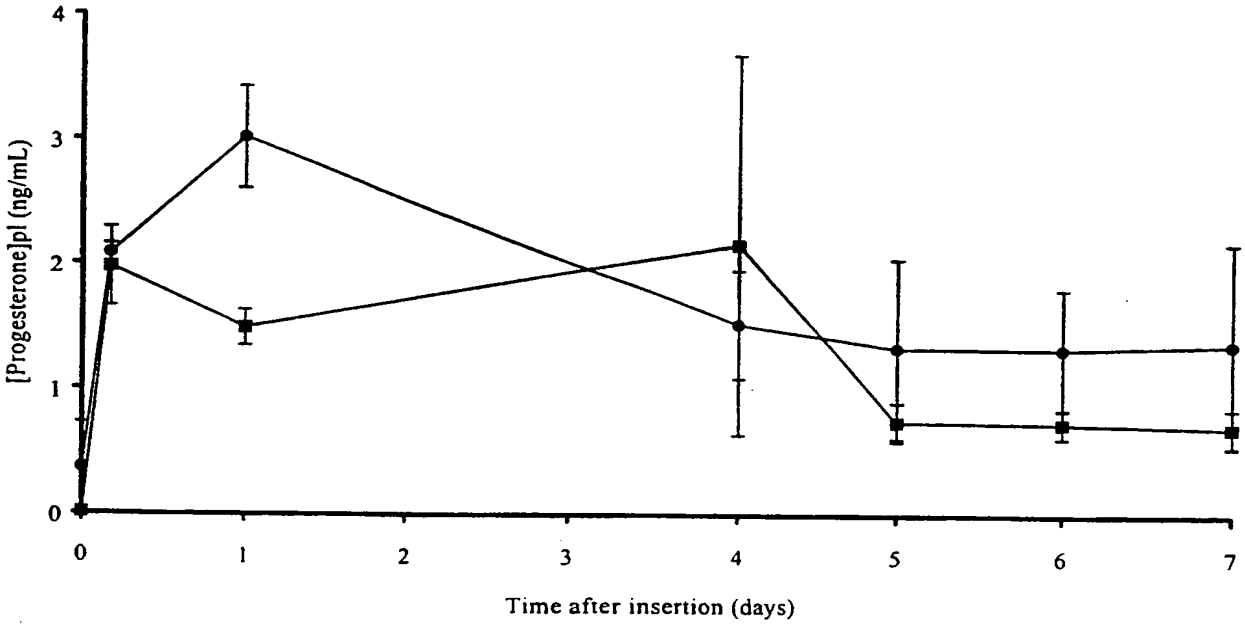
[Progesterone]pl (ng/mL)
0
1
2
3
4
0
1
2
3
4
5
6
7
Time after insertion (days)

FIGURE 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ 98/00169

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61D 19/00; A61F 6/08; A61K 9/02, 47/06, 47/30; A61M 31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: A61D 19/-; A61F 6/-; A61K 9/-, 47/-; A61M 31/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT
JAPIO

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5116619 A (GRECO et al) 26 May 1992 Column 3 lines 43-66	1-17,19-23
E,X	WO 98/53758 A (DEC INTERNATIONAL NZ LTD) 3 December 1998 Page 2 line 28-page 8 line 24, page 16 lines 11-12	1-17,19-23
X	US 4732763 A (BECK et al) 22 March 1988 Column 15 line 48-column 16 line 25	1-17,19-23
X	WO 97/34932 A (BRITISH TECHNOLOGY GROUP LTD) 25 September 1997 Page 8 lines 9-18, page 11 lines 1-6, page 15 lines 4-9 and page 16 lines 13-25	1-17,19-23

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 March 1999	29 MAR 1999
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929	Authorized officer **JOHN HO** Telephone No.: (02) 6283 2329

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ 98/00169

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 5739176 A (DUNN et al) 14 April 1998 Column 2 line 55-column 3 line 29, column 6 lines 45-57	1-17,19-23
X	WO 93/24154 A (FUISZ TECHNOLOGIES LTD) 9 December 1993 See claims 1-26, page 16 lines 12-18	1-17,19-23
X	EP 388234 A (CARTER HOLT HARVEY PLASTIC PRODUCTS GROUP LTD) 19 September 1990 Entire document	1-17,19-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ 98/00169

Box 1 Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: **18**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 18 purports a method of manufacture of an intravaginal device. However, no method steps are defined in this claim.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/NZ 98/00169

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	5116619	US	5084277				
WO	98/53758	AU	79414/98				
US	4732763	AU	51696/79	BE	879442	CA	1143289
		CH	645545	DE	2940146	FR	2439014
		GB	2034182	IL	58471	IT	1124572
		JP	55055114	NL	7907432	NZ	191837
		PH	25638	SE	7908520	ZA	7905549
		US	4585651	US	4756907		
WO	97/34932	AU	20369/97				
US	5739176	AU	45017/89	AU	50677/93	BR	8907686
		DK	572/91	EP	436667	EP	773034
		IL	91850	IL	107393	NO	911277
		US	4938763	WO	90/03768	ZA	8907511
		US	5278201	US	5278202	US	5340849
		US	5632727	US	5725491	US	5733950
		AU	31174/93	CA	2091552	EP	560014
		JP	6007423	US	5792469		
WO	93/24154	AU	44058/93	EP	746342	US	5518730
EP	388234	AU	51247/90	NZ	228382	US	5062829

END OF ANNEX